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EDITORIAL

Toward personalized therapy of chronic hepatitis B

Hepatitis B e antigen seroconversion improves disease outcome

Evidence from natural history

During the natural history of chronic hepatitis B virus (HBV) infection, the loss of serum hepatitis B e antigen (HBeAg) and the development of anti-HBe antibodies (HBeAg seroconversion) make a transition from the immune-clearance phase of disease to the inactive carrier state. Clinical studies on the natural history involving patients with HBeAg-positive chronic hepatitis B (CHB) have demonstrated that HBeAg seroconversion confers improved outcomes, including a sustained reduction in HBV DNA levels, a regression of fibrosis, a lower risk for cirrhosis and hepatocellular carcinoma and a higher incidence of complication-free survival [1–3]. Hsu et al reported on the natural course of chronic HBV infection after spontaneous HBeAg seroconversion in 283 patients [2]; the estimated annual incidence of cirrhosis and hepatocellular carcinoma development was 0.9% and 0.2%, respectively, during a mean follow-up of 8.6 years. Another study involving patients with perinatally acquired chronic HBV infection has shown that spontaneous HBeAg seroconversion occurring at age 15–35 years is associated with a low rate of progression to cirrhosis, whereas delayed seroconversion (after age 40 years) confers a poorer prognosis [4]. Thus, the younger the age at which HBeAg seroconversion occurs, the better the outcome.

Evidence from antiviral therapy

A finite course of pegylated interferon (PegIFN) therapy is associated with higher HBeAg seroconversion rates at the end of treatment compared with 1 year of oral nucleoside/nucleotide analogue (NA) therapy (~27% of PegIFN vs. ~21% of NA) [5,6]. The HBeAg seroconversion rate increased to 33% and to 48% when assessed at 6 months and 12 months, respectively, after the end of PegIFN treatment [5,7]. By contrast, HBeAg seroconversion is usually not durable after 1 year of lamivudine therapy [8]. The lack of durability may result from the failure of lamivudine to completely suppress viral replication and the selection of drug-resistant viral mutants. Our study has demonstrated that HBV genotype B infection, younger (age $<$ 36 years) and consolidation therapy (additional 6–12 months' treatment) after HBeAg seroconversion can improve the post lamivudine treatment durability [9]. The newer oral NAs such as entecavir or tenofovir have shown greater efficacy in profoundly lowering HBV DNA levels, but this enhanced efficacy has not been associated with a concomitant increase in HBeAg seroconversion rate after 1 year of therapy [10]. Data from long-term follow-up studies of continuous oral NA treatment showed that HBeAg seroconversion increased over time [10]. Treatment-induced HBeAg seroconversion has also been shown to confer favorable outcomes and is a strong predictor of prolonged survival between Caucasian and Asian patients [11]. It is now evident that HBeAg seroconversion in associated with polymerase chain reaction-undetectable serum HBV DNA levels is an achievable goal with oral NA treatment and can provide the possibility of improved outcomes with a finite course of therapy for individuals with HBeAg-positive CHB. Thus, a finite course of NA therapy may induce sustained HBeAg seroconversion and provide full immunologic control of disease in patients who would otherwise experience delayed seroconversion, high viral load, and increased risk for the progression of liver disease.

Strategy to maximize HBeAg seroconversion during a finite therapeutic course

The guideline of the CHB reimbursement policy of the National Health Insurance administration in Taiwan demonstrated that the therapeutic period of NA in treating HBeAg-positive patients is 3 years. If patients achieved HBeAg loss during NA treatment, they could take NA for an additional one year of therapy as the consolidation phase. Clearly, the

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physician has the responsibility to treat HBeAg-positive patients at the right time to maximize the possibility of HBeAg loss or seroconversion within the 3-year therapeutic period. Hence, based on personal pretreatment characteristics and on-treatment virological response during NA therapy are crucial for patients to achieve HBeAg seroconversion within a finite period. This is called personalized therapy. In this issue of *Advances in Digestive Medicine*, Su et al [12] reported a multicenter study concerning the efficacy of entecavir therapy in HBeAg-positive patients in Taiwan. They treated 132 HBeAg-positive naïve patients with oral entecavir 0.5 mg daily. The 2-year cumulative HBeAg loss rate was 33.3%. Multivariate analysis after adjustment for age, gender, and alanine aminotransferase (ALT), they found younger age and female gender were two independent predictors to HBeAg loss. Furthermore, the HBeAg loss rate at 2 years was 46% in younger patients and increased up to 73% in young female patients. Recently, Chan et al [13] reported the effects of tenofovir disoproxil fumarate in HBeAg-positive patients within immune tolerance phase. They also found that female gender was an independent baseline factors to predict the serum HBV DNA undetectable at 192 weeks. In addition, our earlier study [14] found increased pretreatment ALT levels and lower HBV DNA could predict a higher probability of HBeAg loss after 1 year of treatment with lamivudine. Zeuzem et al [15] found that the early on-treatment response by non-detectable serum HBV DNA at treatment week 24 is the strongest predictor for optimal outcomes (HBeAg seroconversion, 52%; drug resistance, 1.8%) at 2 years during telbivudine therapy . Obviously, the baseline characteristics and early on-treatment responses are useful in maximizing the possibility of HBeAg loss or seroconversion during NA treatment. Physicians should be aware of the baseline features of serum HBV DNA, ALT, age, gender, and HBV genotype prior to NA treatment and do on-treatment monitoring of serum HBV DNA at 24 weeks during NA treatment to maximize the possibility of HBeAg loss or seroconversion and to accomplish the personalized therapy of patients with CHB.

Conflicts of interest

The author declares no conflicts of interest.

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